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10/617,350	07/11/2003	Ranga R. Namburi	27493U	2736

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EXAMINER	
ANDERSON, JAMES D	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/617,350	NAMBURI ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-13 and 15-42* is/are pending in the application.

4a) Of the above claim(s) *9-13 and 24-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,15-23 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-7, 9-13, and 15-42 are presented for examination

Applicants' amendment filed 12/26/2007 has been received and entered into the application. Accordingly, claims 1, 2, 5, 7, and 17 have been amended, claims 8 and 14 have been cancelled, and claim 42 has been added.

Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Status of the Claims

Claims 1-7, 9-13, and 15-42 are currently pending. Claims 9-13 and 24-41 remain withdrawn from consideration. Accordingly, claims 1-7, 15-23, and 42 are presently under examination and are the subject of this Office Action.

Response to Arguments

Applicant's arguments with respect to claims 1-8, 14-16, and 18-23 as being obvious over Gilis *et al.* and Ishibashi *et al.* in view of Mathir *et al.* have been considered but are moot in view of the new ground(s) of rejection. However, in order to provide a complete prosecution history, the Examiner addresses Applicants' arguments herein.

Firstly, Applicants argue that the Gilis *et al.* reference specifically teaches that the solvent mixture should comprise at least 50% by weight of dichloromethane and does not disclose a working solution containing both the drug and water, as required by the present claims.

Secondly, Applicants argue that the Ishibashi *et al.* reference teaches compositions formed by spraying a polymeric layer on top of a *drug-containing core* whereas the presently claimed process requires both drug and the polymer in the same layer.

Thirdly, Applicants argue that the Mathir *et al.* reference differs from the presently claimed working solution because it does not contain both the drug and water.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In this case, Applicants attack the cited references individually, pointing out how specific claim limitations are not met by each individual reference. However, as noted in the previous Office Action, the claims differ from Gilis *et al.* only in the fact that Gilis *et al.* does not disclose a working solution containing water, alcohol and/or acetone, rather a working solution containing dichloromethane and ethanol. In other words, Gilis *et al.* teach all of the limitations of the instant claims except for the composition of the claimed working solution that is used to spray a coating on the claimed core particles. While Ishibashi *et al.* teach spraying drug-containing particles with a polymeric layer, the skilled artisan would recognize that such a coating process could be used to apply a coating solution to particles that do not contain drug. Accordingly, Ishibashi *et al.* is provided as evidence that ethanol and/or acetone were known in

the art as solvents used to dissolve hydrophobic organic compounds and water-soluble polymers for the purpose of coating core particles.

The Examiner herein further cites **US 2003/0211168 A1** (Published Nov. 13, 2003; Filed Feb. 19, 2001) and **USP No. 6,245,351 B1** (Issued Jun. 12, 2001; Filed Mar. 4, 1997), which both teach that solvents for coating solutions may be water, an organic solvent, or mixtures thereof.

As such, when viewed as a whole, it would have been obvious to one of ordinary skill in the art that the coating solution used to spray coat core-particles could be readily modified by using different solvent systems. The skilled artisan would have been imbued with at least a reasonable expectation that any solvent system capable of dissolving a hydrophobic drug and water-soluble polymer would be effective for spray coating a drug onto core particles and would have been highly motivated to try different combinations of solvents for such a purpose, especially solvents and solvent systems that were known to dissolve both hydrophobic organic compounds and water-soluble polymers as taught in US 2003/0211168 A1 and USP No. 6,245,351 B1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1-6, 15-16, 18-23, and 42 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Gilis *et al***. (WO 00/03697; Published Jan. 27, 2000) (cited by Applicants in IDS filed 12/22/2003) and **Ishibashi *et al***. (U.S. Patent Application Publication No. US 2003/0012815 A1 (Published Jan. 16, 2003; Filed Jan. 26, 2001) (previously cited by the Examiner) in view of **Lynenskjold *et al***. (US 2003/0211168 A1; Published Nov. 13, 2003; Filed Feb. 19, 2001) (newly cited) and ***Nara et al***. (USP No. 6,245,351 B1; Issued Jun. 12, 2001; Filed Mar. 4, 1997) (newly cited).

The instant claims recite a method of manufacturing a water-insoluble azole antifungal dosing form. Said method comprises a single phase working solution of active agent, water, a

water-soluble polymer and a solvent, wherein the solvent is selected from an alcohol, acetone and mixture thereof. The working solution is combined with core particles to produce active agent coated particles.

Gilis *et al*. disclose pellets having a core coated with an antifungal and a polymer (Abstract). With respect to solvents used in forming coated core particles, the reference discloses that dichloromethane and methanol are both Class 2 solvents whose presence in pharmaceutical products should be limited (page 2, lines 28-30). Specifically, the pellets disclosed in Gilis *et al*. comprise: a) a central, rounded or spherical core having a diameter of about 710-1190 μM); b) a coating film of a water-soluble polymer and an antifungal agent; and c) a seal-coating polymer layer, characterized in that the residual solvent levels in said pellets is within limits set by the ICH, that is, the concentration of dichloromethane is less than 600 ppm, most preferably less than 250 ppm (page 4, lines 24-32). Accordingly, Gilis *et al*. disclose using ethanol as an alcoholic co-solvent that is necessary for applying the drug coat layer to the cores (page 4, lines 34-35), thus meeting the limitations of claim 15. Water-soluble polymers include those recited in instant claim 16, for example, hydroxypropyl methylcellulose, polyvinylpyrrolidones and methacrylates (page 6, line 23 to page 7, line 3). Such polymers are disclosed to have an apparent viscosity of 1 to 100 mPas when dissolved in a 2% aqueous solution, thus reasonably encompassing the limitations of instant claim 4 (page 5, lines 32-34). With respect to the composition of the core particles recited in instant claims 18-19, Gilis *et al*. disclose identical core particles composed of, for example, mannitol or microcrystalline cellulose (page 5, lines 8-19). Preferred antifungal agents for use as drugs in the drug-coating layer are lipophilic azole antifungals, in particular itraconazole (page 7, lines 10-11). The instantly

claimed weight ratio of active agent to polymer is obviated by those disclosed at page 7, lines 15-30, for example, 1:1 to 1:5. With respect to the limitations of instant claim 22 wherein an external coating is applied to the drug coated spheres, Gilis *et al.* disclose such an external coating at page 8, lines 28-32. The addition of surfactants as recited in instant claim 3 is disclosed at page 9, lines 1-4. A drying step as recited in claim 1 is disclosed at page 10, lines 32-38).

The reference thus clearly suggests a process of forming drug-coated particles comprising the same steps as those instantly claimed. Further, Gilis *et al.* suggest that the dichloromethane content of the coating should be limited. As such, Gilis *et al.* provide the motivation to use a solvent other than dichloromethane to formulate a coating solution for coating core particles. Gilis *et al.* differ from the claims with respect to the solvents used in the coating solution.

However, Ishibashi *et al.* disclose drug-containing core substance having a multi-layered coating layer (Abstract). With respect to the coating solution used to coat the disclosed core particles, the reference discloses that the solvent system should dissolve both the hydrophobic organic compound and water-soluble polymer (page 6, ¶ [0057]). Suitable solvents include alcohols such as ethanol as well as ketones such as acetone (*id.*). The reference thus teaches that ethanol and acetone are suitable solvents for applying a coating solution to a core particle. The reference does not teach coating solutions additionally comprising water as instantly claimed.

However, Lynenskjold *et al.* teach a process for the production of drug carrier pellets comprising spray-drying a solution of a physiologically tolerable cellulosic binder containing an active drug (Abstract; Example 5). With respect to active drug substances coated onto the spray-dried pellets, the inventors teach that the antifungal, ketoconazole, as recited in claim 42, is one

such active drug substance (page 4, [0046]). The active drug substance will generally be applied to the spray-dried pellets in the form of a solution or dispersion in a physiologically tolerable solvent or solvent mixture, optionally incorporating other components such as binders, sweeteners, pH modifiers, antioxidants, etc. (page 4, [0050]). The coatings may also include further components, including antiadhesives, which are reasonably interpreted as surfactants as recited in claims 3 and 17 (page 5, [0057]). With respect to the coating solutions, while the use of aqueous solutions or dispersions is preferred, organic solvents such as ethanol and acetone as recited in the instant claims may also be used (page 5, [0058]). Methylene chloride, as taught in Gilis *et al*. cited *supra*, may be used but is generally not preferred (*id*.).

Similarly, Nara *et al*. teach solvents for coating solutions may be water, an organic solvent, or mixtures thereof (col. 6, lines 34-35). The organic solvent may be any organic solvent capable of dissolving a water-insoluble substance, such as ethanol or acetone as recited in the instant claims (col. 6, lines 38-46). Water and its mixture with an organic solvent are "preferably used as solvent of coating composition" (col. 6, lines 47-48).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use any suitable solvent system, especially an aqueous-based solvent system, to provide a working solution for coating core particles. In the instant case, the skilled artisan would have been imbued with at least a reasonable expectation that a solvent system consisting of water and alcohol or acetone or mixtures thereof would be effective in dissolving both a water-soluble polymer as well as a hydrophobic active agent such as ketoconazole. The Examiner also notes that acetone is well known in the art as an organic solvent suitable for dissolution of organic compounds. Further, coating core particles with an active agent is a well-

known process as evidenced by the cited references. Applicants' process of coating such particles differs from Gilis *et al.* in the composition of the working solution. However, as discussed *supra*, modifying the working solution of Gilis *et al.* so as to provide dissolution of both a hydrophobic active agent and a water-soluble polymer, while at the same time eliminating methylene chloride from the solution, would require nothing more than identification of solvents suitable for such a purpose. To this point, Ishibashi *et al.* disclose that acetone and ethanol are solvents that may effectively dissolve both hydrophobic organic compounds and water-soluble polymers. Further, Lynenskjold *et al.* and Nara *et al.* both teach that aqueous solutions or aqueous solutions containing an additional organic solvent such as ethanol or acetone are suitable for use in coating core particles. Gilis *et al.* and Lynenskjold *et al.* provide the motivation to use a solvent other than dichloromethane wherein they disclose that the dichloromethane content of the coating should be limited.

With respect to instant claim 2, which recites that the pH of the working solution is adjusted to solubilize the active agent, such a method step would have been obvious to the skilled artisan. For example, many drugs have pH-dependent solubility. As such, if the drug being dissolved in the working solution is insoluble at the pH of the solution, the skilled artisan would be motivated to adjust the pH so as to fully solubilize the active agent. Further Lynenskjold *et al.* teaches that a pH modifying agent may be added to the coating solution disclosed therein.

With respect to instant claim 6, which recites specific ratios of water to working solution, it is well within the level of ordinary skill in the art to determine optimal working ranges of prior art processes and compositions. As such, because an aqueous-based coating solution is *prima*

facie obvious as discussed *supra*, determining the optimum ratio of water to, for example, ethanol or acetone in such coating solutions, would require no more than routine optimization.

Accordingly, the claims are deemed properly rejected as being obvious over Gilis *et al.* and Ishibashi *et al.* in view of Lynenskjold *et al.* and Nara *et al.* who provide the teaching, suggestion and motivation to use any suitable solvent system in order to provide a working solution for coating core particles. Coating core particles with azole antifungal active agent containing coating solutions was clearly well known in the art as evidenced by Gilis *et al.* In fact, the only difference between the prior art and the claims is the composition of the coating solution used to dissolve a water-soluble polymer and azole antifungal agent. However, when the prior art is viewed as a whole, it would have been obvious to one of ordinary skill in the art that the coating solution used to spray coat core-particles could be readily modified by using different solvent systems. The skilled artisan would have been imbued with at least a reasonable expectation that any solvent system capable of dissolving a hydrophobic drug and water-soluble polymer would be effective for spray coating a drug onto core particles and would have been highly motivated to try different combinations of solvents for such a purpose, especially solvents and solvent systems that were known to dissolve both hydrophobic organic compounds and water-soluble polymers as taught in Ishibashi *et al.*, Lynenskjold *et al.,* and Nara *et al.*.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Gilis *et al***. (WO 00/03697; Published Jan. 27, 2000) (cited by Applicants in IDS filed 12/22/2003), **Ishibashi *et al***. (U.S. Patent Application Publication No. US 2003/0012815 A1 (Published Jan. 16, 2003; Filed Jan. 26, 2001) (previously cited by the Examiner), **Lynenskjold *et al***. (US 2003/0211168

A1; Published Nov. 13, 2003; Filed Feb. 19, 2001) (newly cited), and ***Nara et al.*** (USP No. 6,245,351 B1; Issued Jun. 12, 2001; Filed Mar. 4, 1997) (newly cited) as applied to claims 1-6, 15-16, 18-23, and 42 above, and further in view of **Vladyka *et al.*** (USP No. 6,497,905 B1; Issued Dec. 24, 2002; Filed Mar. 20, 2000) (newly cited).

Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* teach as applied *supra* and are here applied to claim 7 in the same manner. The references do not teach the amorphous form of an azole antifungal agent as recited in claim 7.

However, Vladyka *et al.* teach that members of the class of azole antifungal agents such as ketoconazole and itraconazole have very low solubility in aqueous media and will benefit from the method of conversion to the amorphous state (col. 5, lines 36-43).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to provide the claimed azole antifungal agent in the amorphous state because Vladyka et al. teach that these agents having low aqueous solubility will benefit from providing them in their amorphous state. The skilled artisan would reasonably expect that an azole antifungal agent in its amorphous state will exhibit increased solubility (Vladyka et al., col. 5, lines 20-25) in the aqueous coating solutions as motivated and suggested by Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* as discussed *supra*.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Gilis *et al.*** (WO 00/03697; Published Jan. 27, 2000) (cited by Applicants in IDS filed 12/22/2003), **Ishibashi *et al.*** (U.S. Patent Application Publication No. US 2003/0012815 A1 (Published Jan. 16, 2003; Filed Jan. 26, 2001) (previously cited by the Examiner), **Lynenskjold *et al.*** (US 2003/0211168

A1; Published Nov. 13, 2003; Filed Feb. 19, 2001) (newly cited), and ***Nara et al.*** (USP No. 6,245,351 B1; Issued Jun. 12, 2001; Filed Mar. 4, 1997) (newly cited) as applied to claims 1-6, 15-16, 18-23, and 42 above, and further in view of **Martindale: The Complete Drug Reference** (Pharmaceutical Press, London, 2002, pages 1344-1349).

Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* teach as applied *supra* and are here applied to claim 7 in the same manner. The references do not teach the specific surfactants as recited in claim 17.

However, Martindale teaches that surfactants are compounds that can reduce the interfacial tension between two immiscible phases (page 1344), specifically teaching that polysorbates (20, 40, 60, and 80), polyoxyl castor oils, poloxamers, and sorbitan esters (*e.g.*, sorbitan laureate, sorbitan palmitate, and sorbitan stearate) are suitable for use as surfactants in the manufacture of pharmaceuticals (pages 1346-1349).

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use any known surfactant, such as those taught by Martindale, in the manufacture of azole antifungal-coated particles. Gilis *et al.* teach that surfactants can be incorporated in pharmaceutical preparations comprising azole antifungal agents. As such, the skilled artisan would have been imbued with at least a reasonable expectation that the surfactants taught in Martindale would be amiable for use in the coating methods suggested and motivated by the cited references.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
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